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The Synthetic Antimalarials: Atabrine[†] and Plasmochin^{††}

By C. V. WILSON*

THE systematic search for antimalarials started in Germany about 1920, and resulted in the discovery of plasmochin in 1924 and of atabrine in 1930. Since then a very large number of related compounds have been synthesized, and though it is possible that better ones are known and are in use today, they have not yet been announced. Atabrine is the more useful of the two compounds, for it is effective against more forms of the bacilli and is less toxic.

The procedure used in the large-scale

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[†]Atabrine is the American name. British, French and German equivalents are Mepacrine, Quinacrine, and Atebrin, respectively.

^{††}Plasmochin is the American, Pamaquin the British, and Plasmoquine the German name for 6-methoxy-8(1-methyl-4-diethylaminobutylamino) quinoline.

manufacture of atabrine consists in condensing 2,4-dichlorobenzoic acid, (obtained from the 2,4-chloroaminotoluenes by the Sandmeyer reaction followed by oxidation) with *p*-anisidine, closing the ring with phosphorus oxychloride, and heating the resulting 2-methoxy-6,9-dichloroacridine with 1-diethylamino-4-aminopentane in anhydrous phenol. See Figure 1, below.

The side-chain intermediate is prepared by condensing diethylaminoethyl chloride (from the corresponding alcohol and thionyl chloride) with the sodium salt of acetoacetic ester, hydrolyzing and decarboxylating the ester to the ketone, and reducing the latter catalytically in the presence of ammonia, as follows on the next page:

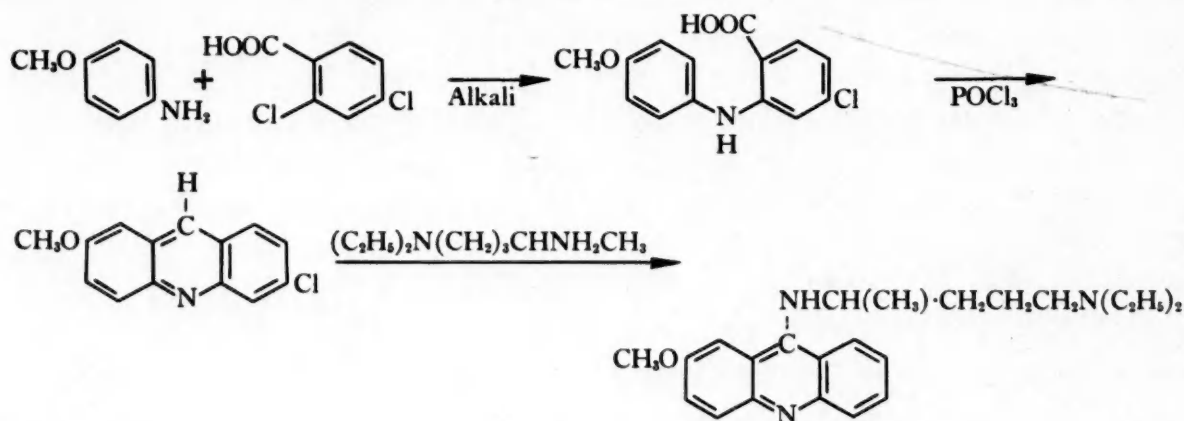
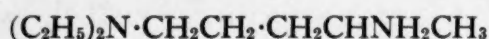
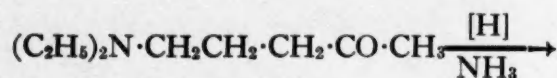
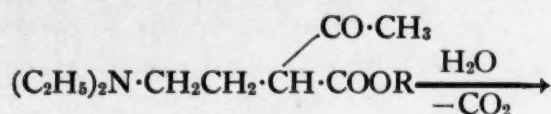
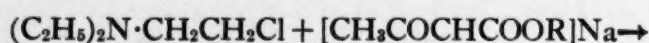


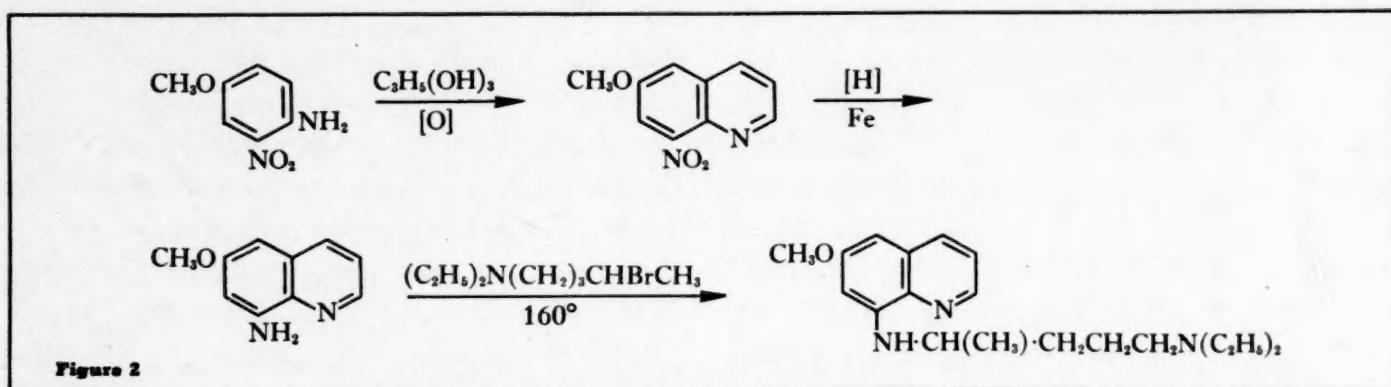
Figure 1



Plasmochin is prepared by condensing 6-methoxy-8-aminoquinoline (obtained by a Skraup synthesis on 3-nitro-4-aminoanisole, followed by reduction) with 1-diethylamino-4-bromopentane. It is purified by distillation in a high vacuum after the removal of unreacted methoxyaminoquinoline by steam distillation. The 1-diethylamino-4-bromopentane is prepared from the same ketone obtained

as an intermediate in atabrine manufacture, by catalytic reduction to the alcohol, followed by bromination (Figure 2).

It is obvious from the formulas that many modifications of both substances are possible, for the acridine and quinoline nuclei may be substituted with many different groups, and the nature of the substituted amino side-chain can be varied indefinitely. However, no outstanding results have yet been reported, with the possible exception of a compound (R-63) said by Robinson to be much more potent than plasmochin. This compound, the structure of which is still unknown, is made by treating 6-methoxy-8-aminopropylaminoquinoline with γ -bromopropylphthalimide.



Linear Polynuclear Hydrocarbons

By C. F. H. ALLEN*

POLYNUCLEAR hydrocarbons are benzologs of benzene, the simplest being naphthalene. This hydrocarbon has two monobenzologs; in one, anthracene, the three benzene rings are in a straight line. This arrangement is said to be *linear*. The other is phenanthrene, in which the arrangement is *angular*. Because of its convenience, the term, *linear polynuclear hydrocarbons*, has come to signify linear benzologs of anthracene; they have been grouped according to certain properties, especially color. Most of these properties are shown to a lesser degree by anthracene. The linear hydrocarbon having four benzene rings is naphthacene, or tetracene ($\text{C}_{18}\text{H}_{12}$); the nomenclature is regular thereafter, e.g., pentacene, hexa-

cene, heptacene. The positions on the ring are numbered clockwise, starting at the top carbon on the right-hand ring.

Naphthacene occurs in small amounts in coal tar; it persists as an impurity in many other polynuclear hydrocarbons isolated from coal tar, and may be responsible for their yellow color. The other linear compounds are obtained by synthetic methods.

The syntheses require the addition of rings in a linear position, which is not an easy process because of the tendency to form angular compounds. The only practical general method involves the use of a phthalic anhydride in a Friedel-Crafts reaction, and cyclization of the *o*-benzoylbenzoic acid thus formed. Advantage is taken of the tendency of reduced ring systems or those bearing suitable

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substituents to close linearly. For example, while the naphthoylbenzoic acids give only *ang*-naphthanthraquinone, *o*-2-tetroylbenzoic acid yields a separable mixture of the angular and linear quinones. The linear tetralanthraquinone is then dehydrogenated to naphthacenequinone, and this ring system is further treated according to the type of product desired. The hydrocarbon is most conveniently obtained by a zinc-dust distillation. Ring closure is facilitated by first reducing the $>\text{CO}$ group to $>\text{CH}_2$, as is so often true in the anthracene series. It should be noted that a quinone or ketone is always an intermediate product. This is not a disadvantage, since many substitution products are most readily prepared from the carbonyl compounds. The most convenient preparation of naphthacene itself consists in the zinc-dust distillation of isoethin-dipthalide (a product resulting from the interaction of phthalic and succinic anhydrides). See Figure 1 below.

Pentacene may be obtained by a variant of this synthesis, in which pyromellitic anhydride is reacted with two molecules of benzene, the diaroylbenzoic acid so formed being then cyclized to a diquinone (Mills, 1912), or, more easily, from

phthalic anhydride and leucoquinizarin with subsequent ring closure (Marschalk, 1937) (Figure 2). The quinones are reduced by zinc dust; frequently, the formation of a dihydro compound is a complicating factor in such reductions. Hexacene and heptacene have been secured by Marschalk and by Clar by analogous procedures.

The linear polynuclear hydrocarbon that attracted the most attention was called "rubrene" by its discoverers, Moureu and Dufraisse. It was originally obtained by a complex reaction (e.g., that between an acid chloride and phenylethynyl diphenylcarbinol), which revealed nothing as to its structure. After a prolonged study, Dufraisse showed that rubrene is 5,6,11,12-tetraphenyl-naphthacene, and his conclusions have been verified by several syntheses. At present the most convenient method of preparation is that of Wittig, who devised a procedure for securing the acetylenic carbinol from phenyllithium, ω -bromostyrene and benzophenone.

Several varieties of polyarylated tetracenes and pentacenes are now known. Most of them have been secured by the action of appropriate organometallic compounds upon the linear polynuclear

quinones, by suitable manipulations. Hydroxy- and aminoquinones are also known. Mixtures that are formed by the various methods of synthesis may often be separated by chromatographic adsorption.

The outline structures of these hydrocarbons is usually determined in the quinones, which are easily cleaved to

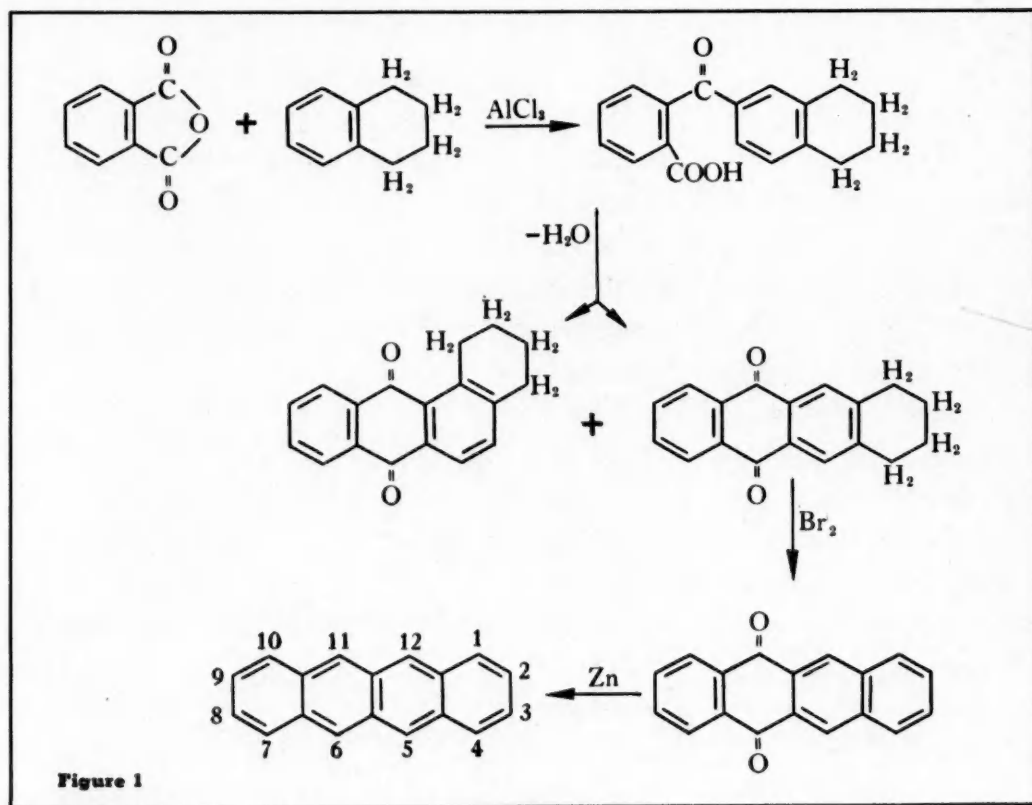
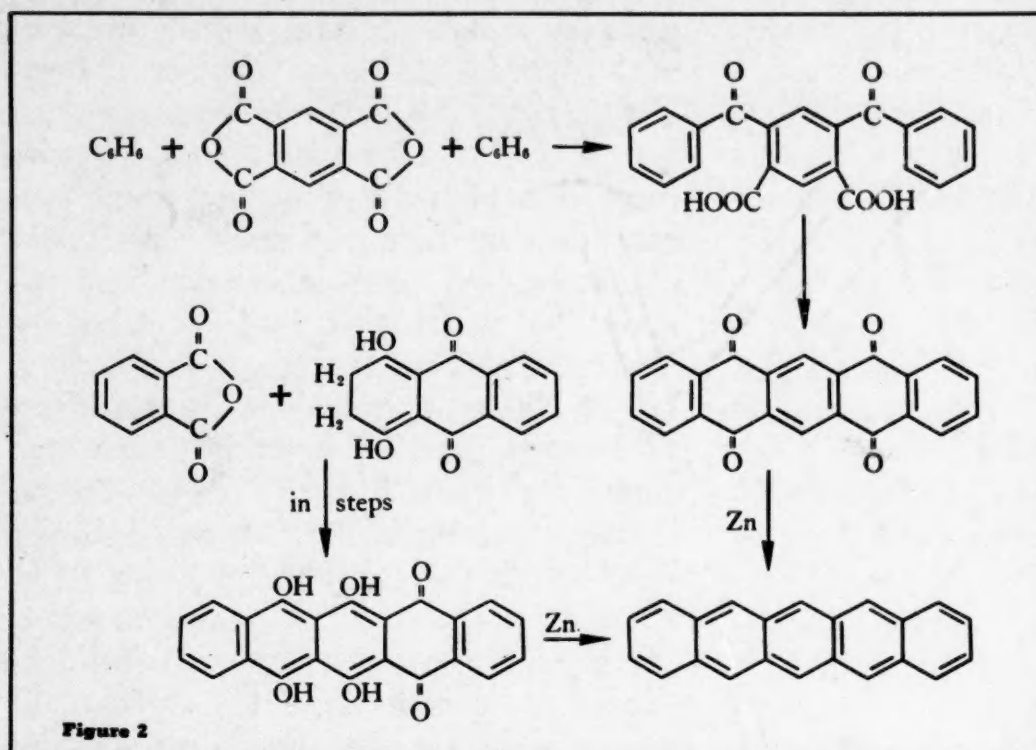


Figure 1



readily recognizable fragments by an alkaline fusion. Now that preparative procedures are largely standardized, the method of synthesis serves as an independent proof of structure; it may be checked, as described later, by observing the characteristic physical properties. The location of the bonds is not so easily settled. It is generally accepted that the preferred bond structures of the two hydrocarbons, naphthalene and pentacene, are those shown. The location of certain bonds in the quinones has been demonstrated by the formation of 1,4-addition products with Grignard reagents.

The most striking physical property of the linear polynuclear hydrocarbons is their deep colors; naphthalene is orange-red, pentacene is reddish-blue, and hexacene and heptacene are green. On account of the colors, Clar suggested that the hydrocarbons were free radicals, diyls. Such an explanation seems improbable, for the substances do not exhibit paramagnetism; at best, the diyl can be considered only as a transitory phase in reactions. The substances have characteristic absorption spectra.

Chemically, these hydrocarbons are very reactive and unsaturated. They combine rapidly, by addition (and are simultaneously decolorized), with oxy-

gen, hydrogen, bromine, and maleic anhydride. (The simplest way to free many coal-tar hydrocarbons from small amounts of naphthalene is to treat them with this anhydride.) The most spectacular property of these hydrocarbons, first noticed with rubrene, is the formation of a colorless photo-oxide ("dissociable oxide")

when benzene or, better, carbon disulfide, solutions are shaken with air in the light. The photo-oxides undergo thermal dissociation with the liberation of oxygen. This photochemical oxidation appears to be a specific reaction of anthracene derivatives, and is not shown by any other group of polycyclic aromatic compounds. The currently accepted structure of these photo-oxides is that of a transannular peroxide in the *meso*-positions, for reduction leads to *meso*-diols.

Oxidation by chemical reagents results in the formation of mono or diquinones. The long conjugated systems of double bonds are partially or completely missing in the quinones, so that the unusual properties associated with the hydrocarbons are no longer encountered.

No carcinogenic activity has yet been observed with the linear polynuclear hydrocarbons.

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